II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-46 and 48-85 were pending and allowed prior to the Office Action dated March 11, 2004. The Action indicates that claims 54 and 83-85 are allowable, as are claims 34 and 48-53 if re-written so as not to depend from a rejected claim.

Claim 34 is amended to correct a typographical error. Claim 41 is amended to eliminate a redundancy. Claim 1 is amended to clarify further the invention. Claims 86-90 have been added. Support for the amendments and new claims can be found in the specification at least at pages 2, lines 4-10; page 14, line 23 to page 15, line 13; page 21, lines 22-26; page 76, line 3 to page 78, line 15, and in originally filed claims 48, 49, 83, 84, and 85. Thus, no new matter has been added.

Claims 1-46 and 48-90 are the subject of this response.

B. Claims 34 and 41-45 Are Definite

The Action rejected claims 34 and 41-45 under 35 U.S.C. §112, second paragraph, as being indefinite failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

Claim 34 has been amended to correct a typographical error. It now recites "a different targeted nucleic acid" instead of "a different targeting nucleic acid," as suggested by the Examiner.

Claim 41 has been amended to delete the word "cellulose," which is listed twice in the claim.

These amendments do not disclaim any subject matter of the claim and were made to correct minor errors to clarify further the claims. As such, claims 34 and 41, as well as claims

42-45 that depend from claim 41, are definite. Applicants respectfully request this rejection be withdrawn.

C. Claims Are Nonobvious

1. Claims 1, 9-11, 14-16, 19-31, 33, and 35-40 Are Not Obvious over Urdea *et al.* in View of Cottingham

The Action rejects claims 1, 9-11, 14-16, 19-31, 33, and 35-40 as unpatentable over 35 U.S.C. §103(a) over Urdea *et al.* (U.S. Patent 5,635,352) ("Urdea") in view of Cottingham (U.S. Patent 5,639,428). More specifically, the Action alleges that Urdea teaches all of the limitations of claim 1 except for discarding the targeted nucleic acid. It contends that this step is well known to those of skill in the art as evidenced by Cottingham. The Action concludes that it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify Urdea to discard the targeted nucleic acid after the assay is completed. It asserts that the ordinary artisan would have been motivated to make this modification because it would have been very time consuming and exceedingly expensive to store and/or repurify the targeted nucleic acid.

The Action further argues that Urdea teaches the limitations of claims 9-11 and 14-16. It acknowledges that none of the cited art teaches the exact location on the target nucleic acid to which the bridging oligos hybridize, but it contends it would have been *prima facie* obvious to the ordinary artisan at the time of the invention that the bridging oligos could be designed, with a reasonable expectation of success, to hybridize anywhere on the targeted nucleic acid. Applicants respectfully traverse this rejection.

The rejection is faulty because in order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations" and "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify

the reference or to combine reference teachings." MPEP §2142. The cited references of Urdea and Cottingham do not teach all of the limitations of claim 1, and none of the other references cited against specific claims corrects this defect. Claim 1 recites:

> 1. A method for depleting a targeted nucleic acid from a sample comprising:
>
> a) incubating the sample with a first bridging oligonucleotide comprising (1) at least one bridging region comprising at least 5 nucleic acid residues and (2) at least one targeting region comprising at least 5 nucleic acid residues, under conditions allowing hybridization between the first targeting region and the targeted nucleic acid;
>
> b) incubating the first bridging oligonucleotide with a capture oligonucleotide comprising a nonreacting structure and a capture region comprising at least 5 nucleic acid residues, under conditions allowing hybridization between the bridging region and the capture region;
>
> c) isolating the targeted nucleic acid from the remainder of the sample, wherein the targeted nucleic acid is depleted from the sample; and,
>
> d) **utilizing the nontargeted nucleic acid in the depleted sample.**

(Emphasis added.) As discussed throughout the application, a goal of the invention is deplete a targeted nucleic acid population using the bridging and capture oligonucleotides in order to effect an enrichment of nontargeted nucleic acids. Claim 1 reflects this by indicating that "the targeted nucleic acid is depleted from the sample" and including a step of "utilizing the nontargeted nucleic acid in the depleted sample." The term "deplete" is defined as "to deprive of contents or supplies" by the Oxford English Dictionary, 2nd ed. (Exhibit A). None of the cited art teaches these elements of the claims. It is clear that the cited references are not concerned with depletion. Urdea involves using nucleic acid molecules to bind analyte that can subsequently be detected. As the Examiner acknowledges by citing Column 27 of Urdea, "the authors teach repeatedly washing the wells of their plates to remove unhybridized nucleic acids." Action at page

3. Clearly, the authors were not "utilizing the nontargeted nucleic acid in the depleted sample," nor did they contemplate such a step.

In fact, the Urdea reference teaches **not** "utilizing the nontargeted nucleic acid in the depleted sample." These authors were concerned with detecting the targeted nucleic acid, not with depleting a sample for targeted nucleic acid and then using the **nontargeted** nucleic acid. Patent law states, "The relevant portions of a reference include not only those teachings which would suggest particular aspects of an invention to one having ordinary skill in the art, but also those teachings which would lead such a person away from the claimed invention." *In re Mercier,* 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975). In this case, Urdea teaches away from the claimed invention because the authors discard the portion of the sample that is the object of the present invention. Consequently, there would be no motivation to combine this reference with *any* other reference so as to achieve the claimed invention.

The reference of Cottingham is said to teach discarding the "tube/composition comprising a molecular biological assay once the assay is completed." However, this reference does not teach the limitation that is missing from Urdea, that of "utilizing the nontargeted nucleic acid in the depleted sample." This reference is simply inapplicable to the claimed invention. Thus, the combination of Urdea and Cottingham fails to present a proper *prima facie* case of obviousness because it does not teach each limitation of claim 1.

Moreover, this combination of references also does not render obvious claims 9-11 and 14-16 because these claims depend directly or indirectly on claim 1.

Applicants also note claims 19-31, 33, and 35-40 are also rejected, but no basis for the rejection is provided. As such, a proper *prima facie* case has not been made because these claims

contain limitations in addition to claim 1. No evidence is provided that any of these limitations is taught or suggested by the cited art.

Accordingly, the rejection of claims 1, 9-11, 14-16, 19-31, 33, and 35-40 is not proper. Applicants respectfully request it be withdrawn.

2. Claims 2-8 and 32 Are Not Obvious over Urdea *et al.* in View of Cottingham and Hogan *et al.*

The Action rejects claims 2-8 and 32 as unpatentable over 35 U.S.C. §103(a) over Urdea in view of Cottingham as applied against claim 1 and 14 and further in view of Hogan *et al.* (U.S. Patent 5,541,308) ("Hogan"). The Action admits that neither Urdea nor Cottingham teaches isolating rRNA. It contends, however, that Hogan is evidence that it was well known in the art at the time of the invention to detect rRNA as a means to detect and/or quantify non-viral organisms. The Action concludes that it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the assay reasonably suggested by Urdea in view of Cottingham, wherein the assay is used to isolate and detect rRNA sequences from both eukaryotic and prokaryotic organisms to detect those organisms recited by Hogan. It also asserts that the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Applicants respectfully traverse this rejection.

As discussed above, the combination of Urdea and Cottingham fails to render obvious claim 1, as well as claim 14, because it does not teach an element of the claimed invention. The cited reference of Hogan does not correct the defect in the *prima facie* rejection based on Urdea and Cottingham. Hogan, like Urdea, involves detecting the targeted nucleic acid, not depleting the targeted nucleic acid.

Moreover, a proper *prima facie* case has not been made because there is no motivation to combine references. The Action contends the motivation arises from the *expectation* that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Whether a person would expect things from the prior art to work together to achieve a particular goal is not the relevant inquiry; instead, the prior art needs to show why a person of ordinary skill in the art would combine their teachings.

Accordingly, the rejection against claims 2-8 and 32 fails as well.

3. Claims 12-13 Are Not Obvious over Urdea *et al.* in View of Cottingham and Weisburg *et al*

The Action rejects claims 12-13 as unpatentable over 35 U.S.C. §103(a) over Urdea in view of Cottingham as applied against claim 1 and further in view of Weisburg *et al.* (U.S. Patent 5,324,632) ("Weisburg"). The Action admits that neither Urdea nor Cottingham teaches isolating a targeted nucleic acid using a bridging or capture region that is polypurine or polypyrimidine. However, it contends that it was well known in the art at the time of the invention, as evidenced by Weisburg, to hybridize two sequences via long stretch of polypurines or polypyrimidines. The Action concludes it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the assay reasonably suggested by Urdea in view of Cottingham, wherein the assay involves a bridging or capture region that is composed only of purines or only of pyrimidines. Applicants respectfully traverse this rejection.

As discussed above, the combination of Urdea and Cottingham fails to render obvious claim 1 because it does not teach an element of the claimed invention. The cited reference of Weisburg does not correct the defect in the *prima facie* rejection based on Urdea and Cottingham. Weisburg, like Urdea, involves detecting the targeted nucleic acid, not depleting the targeted nucleic acid.

Furthermore, there is no motivation or suggestion to combine references. "[T]here must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings" to establish a proper *prima facie* case. MPEP § 2143.01. The Urdea reference evidences that one of skill in the art would lack the motivation to combine Urdea with Weisburg because it specifically indicates that a stretch of nucleotides that is not only purines or pyrimidines constitutes the invention. The Urdea reference specifically states, "Typically, such segments will contain approximately 15 to 50, preferably 15 to 30 nucleotides, and will have a GC content in the range of about 20% to about 80%." Urdea at Col. 6, lines 41-44. Therefore, the requisite motivation to combine is lacking, which is another reason the claims are not rendered obvious by the cited art.

Accordingly, the rejection against claims 12 and 13 fails as well. Applicants respectfully request that this rejection be withdrawn.

4. Claim 17 Is Not Obvious over Urdea *et al.* in View of Cottingham and Lewis *et al*

The Action rejects claim 17 as unpatentable over 35 U.S.C. §103(a) over Urdea in view of Cottingham as applied against claim 1 and 14-15, and further in view of Lewis *et al.* (U.S. Patent 6,270,973) ("Lewis"). The Action admits that neither Urdea nor Cottingham teaches isolating two or more targeted nucleic acids ("multiplexing" according to the Action). However, it contends that it was well known in the art at the time of the invention, as evidenced by Lewis, to multiplex hybridization assays in order to detect two more target nucleic acids simultaneously. The Action concludes it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the assay reasonably suggested by Urdea in view of Cottingham, wherein the assay is multiplexed. Applicants respectfully traverse this rejection.

As discussed above, the combination of Urdea and Cottingham fails to render obvious claim 1 because it does not teach an element of the claimed invention. The cited reference of Lewis does not correct the defect in the *prima facie* rejection based on Urdea and Cottingham. Lewis, like Urdea, is concerned not with depletion of a targeted nucleic acid. Lewis states on the first line of the specification, "The invention relates to nucleic acid detection." Accordingly, the rejection against claim 17 fails as well. Applicants respectfully request that this rejection be withdrawn.

5. Claim 18 Is Not Obvious over Urdea *et al.* in View of Cottingham, Lewis, and Hogan

The Action rejects claim 18 as unpatentable over 35 U.S.C. §103(a) over Urdea in view of Cottingham and Lewis as applied against claims 1, 14-15, and 17, and further in view of Hogan. The Action admits that neither Urdea nor Cottingham teaches an assay in which one of the targeted nucleic acids is the largest rRNA in the sample, while the second targeted nucleic acid is the second largest rRNA in the sample. However, it contends that Hogan teaches detecting either the 18S or 28S rRNA of fungi or the 16S and 23S of bacteria. The Action concludes it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the assay reasonably suggested by Urdea in view of Cottingham and Lewis, wherein both the fungal 28S rRNA and the bacterial 23S rRNA are simultaneously isolated and detected in order to quickly and efficiently determine the cause of a particular illness in a patient. Applicants respectfully traverse this rejection.

As discussed above, the combination of Urdea and Cottingham fails to render obvious claims 1, 14-15 and the combination of Urdea, Cottingham, and Lewis does not render obvious claim 17 because these combinations do not teach an element of the claimed invention. The cited reference of Hogan does not correct the defect in the *prima facie* rejection based on

Urdea/Cottingham and Lewis. Lewis, like Urdea, is concerned with isolating and detecting the targeted nucleic acid and not depleting the targeted nucleic acid. *See e.g.,* Lewis at Col. 1, line 3. As a result, Lewis does not teach the limitation of "utilizing the nontargeted nucleic acid in the depleted sample," which is an element of the claimed invention.

Accordingly, the rejection against claim 18 fails as well. Applicants respectfully request that this rejection be withdrawn.

6. Claims 41-45 Are Not Obvious over Urdea *et al.* in View of Cottingham and Hornes *et al*

The Action rejects claims as unpatentable over 35 U.S.C. §103(a) over Urdea in view of Cottingham as applied against claim 1 and further in view of Hornes *et al.* (U.S. Patent 5,512,439) ("Hornes"). The Action admits that neither Urdea nor Cottingham teaches an embodiment wherein the nonreacting structure comprises a bead with cellulose. However, it contends that it was well known in the art at the time of the invention, as evidenced by Hornes, to use cellulose covered magnetic beads. The Action concludes it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the assay reasonably suggested by Urdea in view of Cottingham, wherein the assay involves cellulose covered magnetic beads. Hornes is also said to teach beads comprising biotin. Applicants respectfully traverse this rejection.

As discussed above, the combination of Urdea and Cottingham fails to render obvious claim 1 because it does not teach an element of the claimed invention. The cited reference of Hornes does not correct the defect in the *prima facie* rejection based on Urdea and Cottingham. Hornes concerns probes used for the "isolation of target nucleic acids and their subsequent manipulation by chemical and/or biochemical techniques." *See* Hornes Col. 1. Again, this reference, like the other cited references, is concerned with isolating and utilizing the targeted

nucleic acid and not the sample that has been depleted for the targeted nucleic acid. Accordingly, the rejection against claims 41-45 fails as well. Applicants respectfully request that this rejection be withdrawn.

7. Claim 46 Is Not Obvious over Urdea *et al.* in View of Cottingham, Hornes and Shuber *et al.*

The Action rejects claim 46 as unpatentable over 35 U.S.C. §103(a) over Urdea in view of Cottingham and Hornes as applied against claim 1 and further in view of Shuber *et al.* (U.S. Patent 5,633,134) ("Shuber"). The Action admits that neither Urdea, Cottingham, nor Hornes teaches using a hybridization buffer comprising TMAC or TEAC. However, it contends that it was well known in the art at the time of the invention, as evidenced by Shuber, to use TMAC or TEAC in a hybridization buffer. The Action concludes it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the assay reasonably suggested by Urdea in view of Cottingham and Hornes, wherein the assay involves a hybridization solution including TMAC or TEAC. Applicants respectfully traverse this rejection.

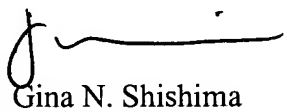
As discussed above, the combination of Urdea in view of Cottingham and Hornes fails to render obvious claim 1 because it does not teach an element of the claimed invention. The cited reference of Shuber does not correct the defect in the *prima facie* rejection based on Urdea, Cottingham and Hornes. Shuber generally concerns "a process for simultaneously detecting the presence or absence of multiple mutations" in a sample. Shuber, Col. 1. Accordingly, the rejection against claim 46 fails as well. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



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Date: June 11, 2004